A REVIEW OF THE ETIOLOGY OF BREAST CANCER

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It is important that physicians be aware of the current theories on the etiology of breast cancer. This article reviews some of the more probable etiologic factors of breast cancer. (*J Natl Med Assoc.* 1993;85:217-221.)

Key words • breast • breast cancer • cancer • etiology of breast cancer

Our patients often ask us why and how they got breast cancer, and what can be done to reduce the risks for their daughters. The concepts of the etiology of breast cancer are changing rapidly, and physicians need to be aware of these changes. This is particularly important for the physician who is called on to offer preventive advice to patients and their families. This article reviews some of the more probable etiologic factors of breast cancer.

Bluntly stated, the etiology of breast cancer remains a mystery. Physicians are still relegated to the role of detectives looking for obscure and contradictory clues. Some of the best known "clues" are: heredity, early menopause, late menarche, late childbirth, obesity, nulliparity, a high-fat diet, oral contraceptives and other exogenous estrogens, age, environmental toxins, alcohol, cigarettes, exposure to radiographs at an early age, and even high socioeconomic status. For example, data from the five San Francisco Bay Area counties indicated that white women from two counties with the highest socioeconomic levels had the highest breast cancer incidence. The increasing incidence of breast cancer in black women is attributed either to better reporting or to progressive improvement in socioeconomic status.[1]

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FAMILIAL CLUSTERING

Familial clustering was first noted in Roman medical literature around 100 AD.[2] The first significant report of a pedigree depicting familial breast cancer and associated malignant neoplasms was published by Broca, who traced the cause of death in 38 members of his wife's family through five generations between 1788 and 1856.[3] Many series since then have shown a strong genetic risk of breast cancer.[4,5]

Available evidence suggests that a woman's risk of developing breast cancer is doubled when she has a mother or sister with the disease and tripled when both her mother and daughter have breast cancer. Studies have shown that the relative risk to first-degree female relatives of patients with premenopausal breast cancer was 3.1, while no increase in risk was observed among relatives of postmenopausal patients. When a patient had bilateral breast cancer, the risk to her first-degree female relatives was increased fivefold. If both conditions applied (ie, the patient was premenopausal and had bilateral disease), the risk to first-degree relatives was increased ninefold.[6,7]

Family history also was found to be the strongest predictor of risk in a review of 122 breast cancer patients and 7304 controls followed for 10 years in the National Health and Nutrition Examination Survey.[5] These figures look very persuasive, but 75% of all breast cancer occurs in women with no family history of the disease.[8] This has led many experts to caution against stressing heredity to avoid creating a false sense of security in some women. Most investigators mention only maternal history of breast cancer as a risk factor, but it seems logical to assume that a history of breast cancer on the paternal side would elevate the risk further.

HORMONAL FACTORS

In patients with a family history of breast cancer, it is uncertain whether other endogenous or exogenous

factors act synergistically with genetic factors. There are some clues to suggest this is the case. Fishman et al[9,10] studied hormone levels throughout the menstrual cycle in 30 young women at high risk for familial breast cancer and compared these with data from 30 matched controls. They found no significant differences in plasma levels of prolactin, luteinizing hormone, follicle-stimulating hormone, estrone, estradiol, or estriol at any stage of menstrual cycle, although a consistent trend toward lower values in all (except estriol) was noted in the high-risk population. Analysis of urinary metabolites, on the other hand, showed that women at high risk of breast cancer excreted significantly less estrone and estradiol compounds than the controls. These investigations were extended to include other estrogen metabolites and showed that when compared with normal controls, women at high risk of breast cancer had significantly lower levels of plasma androsterone sulfate, with a compensatory increase in the urinary estrogen sulfates. Daily analysis showed these differences were most pronounced in the periovulatory period, leading to the conclusion that the risk for breast cancer is associated with an abnormality in estrogen conjugation at a specific time of the ovulatory cycle.

METABOLIC AND SECRETORY FACTORS

Thus, there may be many factors—genetic, cultural, or nonspecific—that influence the cancer risk. For example, Petrakis et al[1,2] postulated that both protection and risk are due to differences in the levels of metabolic and secretory activity of the breast. Women of the dry cerumen genotype (common among Asians and rare among whites) have lower levels of secretory activity in the epithelial cells that line the breast ducts than women of the wet cerumen genotype. The difference may reduce breast cancer risk by protecting the breast duct cells of dry cerumen women from exposure to environmental and dietary carcinogens and cancer-promoting substances secreted into breast ducts from plasma. (They noted that this does not explain the increase in risk that occurs when Asian women migrate to America.)[1,3]

AGE AT FIRST BIRTH

What about effects of age at first childbirth? A British study[15] showed 1003 breast cancer cases occurred in 113 263 women aged 16 to 59. Age at first birth was positively related to increased risk with women giving birth to their first child after the age of 35 being at greater risk than nulliparous women. A review of the National Health and Nutrition Examination Survey also found a greater risk with increasing age at first birth.[6] Bulbrook found a weak association between increased risk and age at first childbirth, but noted a fourfold increase in risk associated with greater age and abnormal parenchymal patterns on mammograms.[12]

OBESITY

A review of 20 341 women showed a significant increased risk of breast cancer associated with obesity.[13] Obese women may have an increased exposure of breast tissue to estrogens because of lower production of 2-OH estrogen compounds, which could result in a relative hyperestrogenic state.[14]

The clues suggesting that dietary fat increases the risk of breast cancer are quite strong. Although some investigators have reported no increase in risk,[13] the weight of evidence points the other way.[14-17] First, mortality data from breast cancer in different countries correlate strongly with per capita consumption of fat. It may be necessary to reduce dietary fat by 80% in order to reduce the risk of breast cancer.[18] Dietary fat affects enteric reabsorption of steroid hormones by influencing the intestinal flora. In addition, obesity and excess fat in the diet are associated with low levels of sex-hormone-binding globulin, leading to higher levels of free sex steroid hormones that would be available to target breast tissue. The excess fat in diet and obesity are also associated with increased production of prolactin and other pituitary hormones. At the same tine, various inconsistencies in the data make any assertion of a causal association between fat and breast cancer premature.[14]

DIETARY FACTORS

There is much uncertainty about the role of diet in the prevention of breast cancer. However, it appears that diet is and will be an important element in reducing the incidence of breast cancer.[19] The National Academy of Sciences concluded that the strongest evidence of an association between dietary components and the incidence of certain cancers is that for fat, particularly where breast cancer is concerned.[18] This would make reduction of dietary fat the most effective method of primary prevention of breast cancer. A comparison of diets in different countries illustrates an inverse relationship between the percentage of calories obtained from fish and the breast cancer rate. Certain clues suggest the omega-3-fatty acids in some fish may have a protective effect.[20]

Energy-adjusted intake of polyunsaturated fat or cholesterol does not influence the morphology of breast tissue seen on the mammogram. Increasing the intake of

carotene and fiber, however, was associated with the reduction of densities noted on mammography. Greater saturated fat intake and reduced carotene and fiber intake may be related to an increase in breast cancer risk through the effects of these nutrients on breast tissue morphology.[21] Breast cancer risk also may be increased by the biological action of specific constituents of fat in the presence or absence of other nutrients. Some of these fat constituents may be naturally present while others may be produced during the food preparation process.[15]

In experimental tumor systems, it can be shown that linoleic acid has tumor-promoting effects that are mediated through eicosanoid production. Feeding fish oil to experimental animals has resulted in decreased concentrations of linoleic and arachidonic acid, and increased concentrations of n-3 eicosapentaenoic acid and docosahexaenoic acid. These n-3 fatty acids antagonize the production of eicosanoids from arachidonic acid and also may influence the 16-alpha-hydroxylation of estrogen. Estrogen is believed to increase the risk of breast cancer. The possible clinical implications of this research are shown by a study in which 25 women at high risk for breast cancer received fish oil while a control group of 25 high-risk women were given vegetable oil. After 4 months, the level of estradiol 16-alpha-hydroxylation was reduced in the women receiving the fish oil, but not in the control group.[22]

EARLY MENARCHE

Early menarche also has been reported to increase the risk of breast cancer. This has not been universally accepted because some investigators have noted only a weak association between early menarche and increased breast cancer risk.[2,12] In any case, women with early menarche appear to have lower levels of circulating sex-hormone-binding globulin and higher levels of estradiol, which may be the central agent in the development of breast cancer.[23] A number of studies have shown a higher mean age at natural menopause among breast cancer patients than in women who do not have breast cancer. Thus, it appears the number of years between menarche and menopause (minus time spent in pregnancy and lactation) is greater in breast cancer patients. Artificial menopause through oophorectomy is associated with a reduction in breast cancer risk if the procedure is done before the age of 40.[1,5,13]

HORMONE REPLACEMENT THERAPY

An evaluation of oral contraceptive and hormone replacement therapy in 20 341 women showed that hormone replacement was associated with a 69% increase in risk of breast cancer. Prolonged hormone replacement did not lead to increased risk except in certain subgroups: women who had previously undergone hormone replacement therapy, women with no maternal history of breast cancer, women with prior benign breast disease, and women who experienced menopause later than the age of 43. The group as a whole showed no increase in risk associated with use of oral contraceptives, although there was a suggestion of increased risk for women who underwent hormone replacement therapy and used oral contraceptives.[24] The length of oral contraceptive use before the age of 25 and early commencement of oral contraceptive use were both associated with a significant increased risk—and so was prolonged use of oral contraceptives before the first pregnancy.[25]

Another study involved comparing 473 breast cancer patients under 45 years of age with 722 matched controls in order to determine whether nulliparous women who had taken oral contraceptives were at greater risk of breast cancer. Results revealed an increased risk for nulliparous women who had used oral contraceptives for more than 8 years.[26] The Cancer and Steroid Hormone Study also revealed an increased risk for nulliparous women who experienced menarche prior to age 13 and who had used the pill for more than 8 years.[27] In addition, Black and Zachrau found oral contraceptive usage associated with breast cancer in 20- to 39-year-old women with a grandmother or aunt who had the disease, and they concluded that familial association "appears to involve an unusual sensitivity" to the female sex hormones in the form of oral contraceptives.[38]

ALCOHOL CONSUMPTION

Most studies of the effects of alcohol indicate a clear association between increased risk of breast cancer and drinking wine or hard liquor.[28] The incidence of breast cancer in 69 000 women who answered a questionnaire about alcohol consumption between 1979 and 1984 showed a progressive increased risk with increasing alcohol consumption.[19] In a 4-year follow-up study of nearly 90 000 US nurses aged 34 to 59, a significant dose-response relationship was found between alcohol and risk of breast cancer.[15] However, there are other studies that show no effect of alcohol on carcinogenesis in the breast.[18]

SMOKING

The association between smoking and breast cancer

also remains controversial. Estrogen metabolism is influenced by many factors, but there is evidence that cigarette smoking can increase 2-hydroxylation of estradiol.[29] Thus, cigarette smoking may be part of a complex process involving a number of factors that result in an increased risk.

LOW-DOSE IRRADIATION

The importance of low-dose irradiation in carcinogenesis depends on age at the time of exposure. There is evidence of increased risk of breast cancer in teenaged and younger females whose breasts were exposed to low-dose irradiation from excess radiation during fluoroscopic examinations or scalp irradiation.[30,31] This increase in risk was found in children aged 5 to 9 who received a dose of approximately 1.6 cGy to the breast from scalp irradiation. Such an effect has not been documented in older women, suggesting that the mature breast is not at the same risk from this source as the maturing breast.[32]

LACTATION

It has long been held that "the breast which has never been called upon for normal function is more liable to become cancerous."[33] Siskind et al have noted that lactation may play a modest or indirect part in reducing the risk of breast cancer for both pre- and postmenopausal women.[34] MacMahon, on the other hand, believed that controlling studies for timing and age of first pregnancy caused any association between lactational history and breast cancer to disappear.[1] Another study by McTiernan and Thomas[35] indicated a definite association between a longer experience of lactation and decreased risk of breast cancer. This trend was particularly marked in premenopausal women. Smigel noted a decreased risk of breast cancer in Chinese women who had breastfed their children for more than 6 months.[36]

SUMMARY

The few clues we have suggest socioeconomic status, heredity, early menopause, late menarche, late childbirth, obesity, nulliparity, high-fat diet, exogenous estrogens, oral contraceptives, age, environmental toxins, alcohol, cigarettes, and radiographs at an early age are all associated with an increased risk of breast cancer.

Better understanding of the etiology of breast cancer will provide physicians with the ability to work with their patients to discuss and develop preventive programs. Even though our present knowledge is limited, we should use all available clues to develop effective preventive programs.

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